PALM INTRANET

Day : Monday
Date: 3/1/2004
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Inventor Information for 10/057620

Inventor Name	City	State/Country
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WADSWORTH, SAMUEL C.	SHREWSBURY	MASSACHUSETTS

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | I

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(FILE 'HOME' ENTERED AT 19:35:54 ON 01 MAR 2004)

FILE 'MEDLINE, CANCERLIT, BIOTECHDS, EMBASE, CAPLUS, BIOSIS' ENTERED AT 19:36:24 ON 01 MAR 2004

```
L1            105 S FACTOR VII AND GENE THERAPY
L2           6313 S FACTOR VIIA
L3             33 S L1 AND L2
L4             31 DUP REM L3 (2 DUPLICATES REMOVED)
L5         470600 S CLEAVAGE OR CLEAVED
L6              3 S L5 AND L1
L7              2 DUP REM L6 (1 DUPLICATE REMOVED)
L8           4260 S FURIN
L9              2 S L8 AND L1
L10             2 DUP REM L9 (0 DUPLICATES REMOVED)

=>
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Nguyen, Dave

From: Auto TrainR
Sent: Wednesday, February 25, 2004 9:47 AM
To: Nguyen, Dave
Cc: Reynolds, Deborah
Subject: Class Registration Confirmation for Dave Nguyen

Dear Dave Nguyen,

This is to confirm that you have registered for the following class:

Course Title: End of the Year Review of CAFC Decisions (1.5hr)
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Registered As: SPE Assigned

Have a nice day!

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Tel: (703) 306-5791 & (703) 306-5792
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4 ANSWER 30 OF 31 MEDLINE on STN

AN 2001222853 MEDLINE

DN PubMed ID: 11127866

TI Blocking the initiation of coagulation by RNA aptamers to **factor VIIa**.

AU Rusconi C P; Yeh A; Lyerly H K; Lawson J H; Sullenger B A

CS Department of Surgery, Duke University Medical Center, Durham, NC 27710, USA.

SO Thrombosis and haemostasis, (2000 Nov) 84 (5) 841-8.
Journal code: 7608063. ISSN: 0340-6245.

CY Germany: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200104

ED Entered STN: 20010502
Last Updated on STN: 20010502
Entered Medline: 20010426

AB The tissue factor/**factor VIIa** complex is thought to be the primary initiator of most physiologic blood coagulation events. Because of its proximal role in this process, we sought to generate new inhibitors of tissue factor/**factor VIIa** activity by targeting **factor VIIa**. We employed a combinatorial RNA library and in vitro selection methods to isolate a high affinity, nuclease-resistant RNA ligand that binds specifically to coagulation **factor VII**/VIIa. This RNA inhibits the tissue factor-dependent activation of factor X by **factor VIIa** . Kinetic analyses of the mechanism of action of this RNA suggest that it antagonizes **factor VIIa** activity by preventing formation of a functional **factor VII**/tissue factor complex. Furthermore, this RNA significantly prolongs the prothrombin time of human plasma in a dose dependent manner, and has an in vitro half-life of approximately 15 h in human plasma. Thus, this RNA ligand represents a novel class of anticoagulant agents directed against **factor VIIa**.

L4 ANSWER 28 OF 31 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:220527 BIOSIS
DN PREV200200220527
TI Long-term expression of activated FVII in vivo following AAV-mediated liver gene transfer: Implications for treatment with continuous infusion of recombinant activated FVII.
AU Margaritis, Paris [Reprint author]; Arruda, Valder R. [Reprint author]; High, Katherine A. [Reprint author]
CS Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA
SO Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 696a. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 3 Apr 2002
Last Updated on STN: 3 Apr 2002
AB A current treatment for acute bleeding episodes in hemophilia A and B patients who have developed inhibitory antibodies to the infused factor (factor VIII and factor IX, respectively), is administration of high doses of recombinant activated human **factor VII** (rFVIIa).
While repeated bolus injections of rFVIIa have been used, experience with continuous infusion of rFVIIa is limited and raises safety concerns regarding occlusive vascular complications resulting from activation of the coagulation system. Here, we investigated the effect of long-term continuous expression of FVIIa in mice at various circulating levels, as part of a **gene therapy** strategy for treatment of hemophilic animals with inhibitors. We engineered a FVII variant that is intracellularly-processed and secreted as activated FVII (FVIIa), by inserting a protein recognition sequence for an intracellular protease at position Arg 152-Ile 153. This FVII variant is predominantly secreted in vitro in a double chain, activated FVII form and has similar in vitro activity and in vivo half-life as recombinant FVIIa, following injection in normal C57BL/6 mice. In order to demonstrate the efficacy of our gene transfer approach, we initially used rFVIIa into hemophilia A and B mice with and without inhibitors, injected at the clinically effective dose of 90 micrograms/kg. We observed a shortening of the prothrombin time (an assay sensitive to FVIIa levels) as early as 15 min, which returned to baseline after 6 hours, indicating that our approach can be used in a hemophilic mouse model. To further study the long-term effect of continuous FVIIa expression, we constructed a recombinant AAV-2 viral vector carrying this FVIIa transgene under the control of a liver-specific promoter and injected vector into the portal circulation in hemostatically normal immunodeficient mice (n=7) at doses ranging from 1.5X1011 vector genomes (v.g.)/mouse to 2.4X1012 v.g./mouse. Mouse plasma was collected and assayed for antigen levels by an ELISA specific for human FVII/FVIIa. Following gene transfer, we observed stable, long-term expression of FVIIa with antigen levels ranging from 150 ng/ml to 950 ng/ml, as assayed over a period as long as 24 weeks post-injection. Throughout the course of these experiments, we did not observe any adverse effects at any doses tested. To further investigate any changes in the activity of the coagulation system in these animals, we assayed plasma samples collected at time points up to 24 weeks for the presence of elevated levels of thrombin-antithrombin III (TAT) complexes. By using an ELISA for TAT that is known to cross-react with murine proteins, we observed TAT levels ranging from 0.8 ng/ml to 20.1 ng/ml, while TAT levels in normal animals were approximately 22 ng/ml. This indicates that the long-term expression of the FVIIa transgene did not result in detectable changes in the mouse coagulation system. Overall, we show that long-term expression of FVIIa can be achieved by AAV gene transfer without thrombotic complications.

More extensive testing will be required to demonstrate the efficacy of such therapeutic strategy in hemophilic animals with inhibitors. These data support the potential of such an approach for hemophilic patients with inhibitors.

L4 ANSWER 27 OF 31 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:713370 CAPLUS
DN 135:277991
TI Modified blood clotting factors for treatment of bleeding or clotting disorder
IN High, Katherine A.; Margaritis, Paris; Camire, Rodney M.
PA Children's Hospital of Philadelphia, USA
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001070763	A1	20010927	WO 2001-US9355	20010322

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-191331P P 20000322

AB The invention provides compns. including modified blood clotting factors, i.e., **Factor VII**, Factor IX, and Factor X, that have a non-native proteolytic cleavage site engineered into them allowing intracellular cleavage and secretion of an active form. The compns. are useful in the methods for treating a bleeding or clotting disorder. For example, gene transfer of modified blood coagulation **factor VIIa** using the AAV-hAAT-ApoE-FVIIa expression vector offers a treatment for hemophilia patients and does not appear to induce production of inhibitory antibodies against FVIIa.

L4 ANSWER 24 OF 31 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN 2003-00809 BIOTECHDS
TI Promoting blood coagulation for treating individuals with blood coagulation defects, e.g. hemophilia A and B, comprises administering a DNA vector encoding a modified **Factor VII** leading to the generation of **Factor VIIa** in vivo;
adeno virus, adeno-associated virus, retro virus or lenti virus vector-mediated gene transfer and expression in host cell for use in blood disease therapy and **gene therapy**
AU SCARIA A; WADSWORTH S C
PA GENZYME CORP
PI WO 2002055110 18 Jul 2002
AI WO 2001-US51391 25 Oct 2001
PRAI US 2001-307492 24 Jul 2001; US 2000-243046 25 Oct 2000
DT Patent
LA English
OS WPI: 2002-583644 [62]
AB DERWENT ABSTRACT:
NOVELTY - Promoting blood coagulation in an individual with a blood coagulation defect, comprising administering to the individual a DNA vector encoding a modified **Factor VII**, which leads to generation of **Factor VIIa** in vivo, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) treating an individual having a blood coagulation defect by administering a composition comprising a first DNA vector which encodes amino acids 1-152 of human **Factor VII**, and a second DNA vector comprising amino acids 153-406 human **Factor VII** and a leader sequence; (2) treating hemophilia in an individual who has developed an inhibitor of Factor VIII or Factor IX by: (a) administering a DNA vector encoding modified **Factor VII**, which leads to generation of **Factor VIIa** in vivo; or (b) administering a composition comprising a first DNA vector which encodes amino acids 1-152 of human **Factor VII**, and a second DNA vector comprising amino acids 153-406 of human **Factor VII** and a leader sequence; (3) a DNA expression vector comprising nucleic acid encoding a modified **Factor VII**, which leads to generation of **Factor VIIa** in vivo; (4) a nucleic acid construct comprising two DNA expression cassettes which together encode **Factor VII**, where the first expression construct encodes amino acids 1-152 of human **Factor VII** and the second expression encodes amino acids 153-406 of human **Factor VII** and a leader sequence; and (5) a nucleic acid construct comprising a polycistronic expression cassette, where the expression cassette comprises nucleic acids encoding the light and heavy chain of **Factor VII** , where the nucleic acids are separated by an internal ribosome entry site.

WIDER DISCLOSURE - Disclosed are host cells comprising a DNA vector with a nucleic acid which encodes a modified **Factor VII** , which leads to generation of **Factor VIIa** in vivo.

BIOTECHNOLOGY - Preferred Method: The modified **Factor VII** in the method of promoting blood coagulation further comprises an amino acid sequence which codes for a signal for precursor cleavage by a cleavage enzyme selected from furin and SK1, at the activation cleavage site of the modified **Factor VII**. When the cleavage enzyme is furin, the amino acid sequence of the signal in the modified **Factor VII** is selected from Arg149-X150-Lys151-Arg152 of human FVII and Arg149-X150-Arg151-Arg152 of human FVII, preferably Arg149-Gln150-Lys151-Arg152 of human FVII. The leader sequence in the method of treating an individual having a blood coagulation defect, is derived from a protein selected from a cytokine, growth factor, colony stimulating factor and a clotting factor. The DNA vector, administered as naked DNA or in association with an amphiphilic

compound, is a viral vector selected from an adenovirus vector, a partially-deleted adenovirus vector, a fully-deleted adenovirus vector, an adeno-associated virus vector, a pseudoadenovirus vectors, a retrovirus vector and a lentivirus vector. The blood coagulation defect is selected from hemophilia A, hemophilia B and **factor VII** deficiency, preferably hemophilia A and B, and the individual having the disease exhibits the presence of inhibitors of FVIII and/or FIX. The DNA vector in the method of treating hemophilia in an individual who has developed an inhibitor of Factor VIII or IX comprises a nucleotide sequence which codes for a signal for precursor cleavage by furin at the activation cleavage site of the modified **Factor VII**. The DNA vector is administered as naked DNA or in association with an amphiphilic compound.

ACTIVITY - Hemostatic. Test details are described but no results given.

MECHANISM OF ACTION - **Gene therapy**; **Factor-VII**-Stimulator.

USE - The methods and compositions of the present invention are useful for treating an individual having a blood coagulation defect, e.g. **Factor VII** deficiency, hemophilia A and B (claimed).

ADMINISTRATION - The dose range of plasmid DNA is 1 microg-1 g, preferably 100 microg-100 mg. The dosage may also be tailored in order to achieve a FVII plasma concentration level of 5-1000 ng/ml. Routes of administration of the modified FVII include intravenous, parenteral, intramuscular, subcutaneous, oral, nasal, inhalational, by implants and/or rectal.

ADVANTAGE - Prior methods of treating bleeding disorders has led to the development of inhibitors to **Factor VII**, which can lead to the ineffectiveness of protein replacement or gene replacement therapies. Other methods using recombinant activated **Factor VII** have been shown to bypass or correct the coagulation defects in hemophiliacs with inhibitors. However, recombinant FVIIa is expensive to manufacture and has a very short half life. The present method using activated FVII delivered via DNA vectors is useful specifically to patients who have developed inhibitors especially to FVII. (44 pages)

L4 ANSWER 25 OF 31 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN 2002-09973 BIOTECHDS
TI New albumin fusion proteins with extended shelf life, useful for treating leukemia, warts, hepatitis, multiple sclerosis and AIDS, comprises therapeutic protein fused to albumin;

recombinant protein gene production via plasmid expression in host cell, polymerase chain reaction, gel electrophoresis useful in disease **gene therapy**

L7 ANSWER 2 OF 2 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN 2002-02325 BIOTECHDS
TI Mutant blood clotting factors useful for treating a bleeding or clotting disorder in a subject, comprising a modified proteolytic **cleavage** site not normally present in the factor;
useful for transgenic animal production and **gene therapy**
AU High K A; Margaritis P; Camire R M
PA Child.Hosp.Philadelphia
LO Philadelphia, PA, USA.
PI WO 2001070763 27 Sep 2001
AI WO 2001-US9355 22 Mar 2001
PRAI US 2000-191331 22 Mar 2000
DT Patent
LA English
OS WPI: 2001-611468 [70]
AB A composition (M) comprising a recombinant polynucleotide (I) that encodes a modified blood clotting factor (MBCF), where the modification comprises a proteolytic **cleavage** site not normally present in the factor, and where the factor is **cleaved** at the **cleavage** site when expressed in an animal cell, is claimed. Also claimed are: a polypeptide (II) encoded by (I); and a kit (II) comprising (M) or (II). Also claimed are: cells encoding (I); and vector incorporating (I). (I) is useful for treating a bleeding or clotting disorder of a subject preferably mammal especially human, having or at risk of having such a disorder, amenable to treatment with **Factor -VII**, Factor-VIII or Factor-IX and is caused by insufficient activity of expression of a vitamin-K dependent procoagulant, or by insufficient platelet aggregation. The disorder comprises hemophilia comprising hemophilia A or B, or **Factor-VII** deficiency, Glanzmann's thrombasthenia or Bernard-Soulier's thrombasthenia. (I) is also useful for decreasing clotting time and for reducing the frequency or severity of bleeding in a subject (claimed). (55pp)

Freeform Search

Database: US Pre-Grant Publication Full-Text Database; US Patents Full-Text Database; US OCR Full-Text Database; EPO Abstracts Database; JPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Term: l11 with l7

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L15	l11 with l7	15	L15
L14	l11 and l8	1	L14
L13	l11 and l7	566	L13
L12	L11 same l8	0	L12
L11	factor VII	2160	L11
L10	L9 and l8	1	L10
L9	cleaved or cleavage	121175	L9
L8	l7 with l6	105	L8
L7	gene therapy	39697	L7
L6	factor VIIa	2292	L6
L5	L4 with l2	32	L5
L4	replication defective or replication incompetent	6146	L4
L3	replication defective replication incompetent	10	L3
L2	immunomodulatory or cytokine	43625	L2
L1	6287557	6	L1

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L8: Entry 105 of 105 File: DWPI Nov 7, 2002

DERWENT-ACC-NO: 2003-428756
DERWENT-WEEK: 200340

Full - [FULL]
Title - [TI]
Citation - [CIT]
Front - [FRO]
Review - [REV]
Classification - [CLAS]
Date - [DATE]
Reference - [REF]
Sequences - [SEQ]
Attachments - [ATT]
Claims - [CLM]
KWIC - [KWIC]
Drwg Desc - [DRAW]
Image - [IMG]

TITLE: Method of inhibiting immune response of host to a gene therapy vector and encoded transgene product, thus allowing persistent expression of transgene, comprises co-administering gene therapy vector with rapamycin

Basic Abstract Text (5):
USE - The method is useful for inhibiting immune response of host to a gene therapy vector (such as an adenoviral vector containing a deletion of adenoviral gene sequences) and encoded gene product such as glucocerebrosidase, alpha-glucosidase A, beta glucosidase, sphingomyelinase, iduronate sulfatase, alpha-glucosidase, alpha -iduronidase, Factor VIIA, Factor VIII or Factor IX. The method thus allows for persistent expression of a transgene encoding any one of above mentioned gene products (claimed). The method has application in treatment protocols of genetic disease patients that mount immune response to protein replacement therapies.

Basic Abstract Text (7):
Preferably, the method is useful for inhibiting immune response in a patient administered with a gene therapy vector, gene therapy vector for treating lipid storage disorders such as lipid storage disorders (LSDs), e.g. Gaucher's disease, Fabry's disease, Niemann-Pick B disease, Hunter's disease, Morquio's disease, Maroteaux-Lamy disease, Pompe's disease, Hurler's-Scheie's disease in its various clinical manifestations, as well as hemophilic factors: factor VIIA, factor VIII and factor IX.

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L15: Entry 4 of 15 File: PGPB Dec 11, 2003

PGPUB-DOCUMENT-NUMBER: 20030229036
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030229036 A1

TITLE: Methods for treating blood coagulation disorders

PUBLICATION-DATE: December 11, 2003

US-CL-CURRENT: 514/44

APPL-NO: 10/ 057620 [PALM]
DATE FILED: October 25, 2001

RELATED-US-APPL-DATA:
Application is a non-provisional-of-provisional application 60/243046, filed October 25, 2000,
Application is a non-provisional-of-provisional application 60/307492, filed July 24, 2001,

[0001] This application claims the benefit of priority under 35 U.S.C. .sctn.119(e) to U.S. Provisional Application Serial No. 60/243,046 filed Oct. 25, 2000 and No. 60/307,492 filed Jul. 24, 2001 respectively. The contents of these applications are hereby incorporated by reference into the present disclosure.

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L15: Entry 5 of 15 File: PGPB Oct 9, 2003

DOCUMENT-IDENTIFIER: US 20030192066 A1
TITLE: Minimal adenoviral vector

Detail Description Paragraph:
[0317] 12. Chuah, M. K. L., T. Vandendriessche, and R. A. Mogan. 1995. Development and analysis of retroviral vectors expressing human factor VII as a potential gene therapy for hemophilia A. Human Gene Ther. 6: 1363-1377.

First Hit

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L15: Entry 7 of 15 File: PGPB Apr 17, 2003

DOCUMENT-IDENTIFIER: US 20030073652 A1
TITLE: Ex-vivo and in vivo factor XII gene therapy for hemophilia A and B

Summary of Invention Paragraph:
[0002] The invention relates to the use of recombinant Factor XII and truncated or mutated forms thereof, in gene therapy for conversion of inactive Factor VII to its active form in the treatment of Hemophelia A and B.

Detail Description Paragraph:
[0030] The adenoviral system with either full length Factor VII, or Factor VII from which the B-domain has been deleted, has been studied intensively. Expression levels using recombinant adenoviral vectors have been optimized in hepatocytes (Andrews et al, 1999), and studied when transfected into factor VII-deficient mice (Connelly et al, 1996; Connelly et al, 1998; Connelly et al, 1999). A minimal adenoviral vector, devoid of all viral genes, has been developed which theoretically avoids the intrinsic toxicity of the adenovirus (Balague et al, 2000). Such "mini-adenoviral" vectors have also been tested with Factor VIII in mice and dogs (Zhang et al, 1999). Ex-vivo gene therapy of primary fibroblasts with adenovirus mediated Factor VII has also been reported. The recombinant gene was placed into the virus in the test tube, and the gene-virus combination transfected into the cell. The cells were then implanted into the spleen of the recipient animal (Zatloukal et al, 1994). Adenovirus-mediated transfer of Factor IX has been associated with dose-limiting toxicity in monkeys (Lozier et al, 1999).

(FILE 'HOME' ENTERED AT 19:51:36 ON 01 MAR 2004)

FILE 'MEDLINE, CANCERLIT, BIOTECHDS, BIOSIS, EMBASE, CAPLUS' ENTERED AT 19:51:52 ON 01 MAR 2004

L1 1898 S FACTOR AND (BLOOD COAGULATION OR HEMOPHILI?) AND GENE THERAPY
L2 3410755 S REVIEW
L3 168 S L2 AND L1
L4 130 DUP REM L3 (38 DUPLICATES REMOVED)
L5 416539 S ADENOVIR? OR RETROVIR?
L6 42 S L5 AND L4

L6 ANSWER 39 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:741527 CAPLUS
DN 131:346059
TI Adeno-associated virus-mediated gene transfer of **factor** IX for treatment of **hemophilia** B by **gene therapy**
AU Herzog, Roland W.; High, Katherine A.
CS Dep. Pediatrics Pathology, Medical Center, Univ. Pennsylvania, Philadelphia, PA, USA
SO Thrombosis and Haemostasis (1999), 82(2), 540-546
CODEN: THHADQ; ISSN: 0340-6245
PB F. K. Schattauer Verlagsgesellschaft mbH
DT Journal; General Review
LA English
AB A **review** with 48 refs. is given on adeno-associated virus (AAV)-mediated gene transfer of **factor** IX for treatment of **hemophilia** B. **Gene therapy** strategies for **hemophilia** B resulted in expression of **factor** IX in mice and scale-up attempts to the canine and dog model were made. Long-term expression of **factor** IX was achieved in dogs, the development of inhibitory antibody was observed in some cases. The potential of the AAV vectors to integrate into chromosomal DNA and the risk of germ-line transmission is mentioned.

L6 ANSWER 38 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:741530 CAPLUS
DN 131:346061
TI Animal testing of **retroviral**-mediated **gene therapy** for **factor** VIII deficiency
AU Greengard, Judith S.; Jolly, Douglas J.
CS Dep. Vaccines Gene Therapy, Chiron Technologies, Emeryville, CA, 94608, USA
SO Thrombosis and Haemostasis (1999), 82(2), 555-561
CODEN: THHADQ; ISSN: 0340-6245
PB F. K. Schattauer Verlagsgesellschaft mbH
DT Journal; General Review
LA English
AB A **review** with 62 refs. is given on animal testing of **retroviral**-mediated **gene therapy** for **factor** VIII deficiency . Advantages and potential disadvantages of **retroviral** vectors, and the status of **gene therapy** for **hemophilia** in animal models is summarized. Own unpublished results are also presented, describing the i.v. injection of nonmurine packaging cell lines with high titers of **factor** VIII vectors in dogs and rabbits, leading to **factor** VIII expression in these animals.

L6 ANSWER 35 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:658526 CAPLUS
DN 136:20
TI Viral vector-mediated **gene therapy** for **hemophilia**
AU VandenDriessche, Thierry; Collen, Desire; Chuah, Marinee K. L.
CS Center for Transgene Technology and Gene Therapy, Flanders Interuniversity Institute for Biotechnology-University of Leuven, Louvain, B-3000, Belg.
SO Current Gene Therapy (2001), 1(3), 301-315
CODEN: CGTUAH; ISSN: 1566-5232
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
AB A **review** with refs. is given. **Hemophilia** A and B are hereditary coagulation disorders that result from functional deficiencies of **factor** VIII (FVIII) or **factor** IX (FIX), resp. Current treatment consists of injections with blood plasma-derived or recombinant clotting factors. Despite the significant clin. benefits of protein replacement therapies, these do not constitute a cure and patients are still at risk of bleeding. Significant progress was made recently in the development of **gene therapy** for **hemophilia** . This was primarily due to the tech. improvements of existing vector systems and the development of new gene delivery methods. Therapeutic and sometimes physiol. levels of FVIII and FIX could be achieved in FVIII- and FIX-deficient mice and **hemophilic** dogs using different types of viral vectors. In these preclin. studies, long-term correction of the bleeding disorders and in some cases a permanent cure was realized. However, complications related to the induction of neutralizing antibodies or viral promoter inactivation often precludes stable phenotypic correction. Several **gene therapy** phase I clin. trials were initiated in patients suffering from severe **hemophilia** A or B. The results from the extensive pre-clin. studies and the preliminary clin. data are encouraging. It is likely that successful **gene therapy** for **hemophilia** will become a reality at the beginning of this new millennium, serving as the trailblazer for **gene therapy** of other diseases

L6 ANSWER 32 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:949415 CAPLUS
DN 139:94509
TI Adeno-associated virus-mediated gene transfer for **hemophilia** B
AU High, Katherine A.
CS Division of Hematology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
SO International Journal of Hematology (2002), 76(4), 310-318
CODEN: IJHEEY; ISSN: 0925-5710
PB Carden Jennings Publishing
DT Journal; General Review
LA English
AB A **review**. **Hemophilia** is the bleeding diathesis caused by mutations in the gene encoding **factor** VIII (**hemophilia** A) or **factor** IX (**hemophilia** B). Currently, the disease is treated by i.v. infusion of the missing purified clotting **factor**. The goal of gene transfer for treating **hemophilia** is to achieve sustained expression of **factor** VIII or **factor** IX at levels high enough to improve the symptoms of the disease. **Hemophilia** has proven to be an attractive model for those interested in gene transfer, and multiple gene-transfer strategies are currently being investigated for the **hemophilias**. The most promising preclin. studies have been with adeno-associated viral vectors (AAV); introduction of AAV vectors expressing **factor** IX into skeletal muscle or liver in **hemophilic** dogs has resulted in the long-term expression of **factor** IX at levels that are adequate to improve disease symptoms. Efforts to translate these findings into the clin. arena have proceeded slowly because of the lack of prior clin. experience with parenteral administration of AAV. In a staged approach, AAV-**factor** IX (AAV-F.IX) was first administered at doses of up to 1.8 + 1012 vector genomes/kg (vg/kg) into the skeletal muscles of men with **hemophilia** B. This trial established the safty of parenteral administration and also showed that general characteristics of AAV transduction were similar in mice, dogs, and humans. In an ongoing trial, AAV-F.IX is being administered into the hepatic circulation of men with severe **hemophilia** B. The goal of these studies is to identify a safe dose that reliably yields circulating levels of **factor** IX >2% of normal levels in all subjects. This goal has already been achieved in the **hemophilia** B dog model; the ongoing study will determine whether a similar result can be achieved in humans with **hemophilia** B.

L6 ANSWER 27 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 97351864 EMBASE
DN 1997351864
TI **Gene therapy** for haemophilia.
AU Smith T.A.G.
CS T.A.G. Smith, Genetic Therapy Inc., 19 Firstfield Road, Gaithersburg, MD 20878, United States
SO Expert Opinion on Investigational Drugs, (1997) 6/11 (1685-1690).
Refs: 43
ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal; General Review
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
025 Hematology
LA English
SL English
AB Progress rewards the development of a **gene therapy** protocol for the treatment of haemophilia has been substantial. Recent achievements include high level clotting **factor** expression in mice, dogs, and monkeys as well as phenotypic correction in both mouse and canine models of haemophilia. Studies using **adenoviral** (Ad) vectors have contributed to much of the recent success. However, the repertoire of gene transfer vehicles being applied to the development of **gene therapy** strategies for haemophilia has expanded. In particular, encouraging data have been generated from studies using recombinant adeno-associated virus (AAV) vectors. Progress toward human clinical trials has been inhibited by host immune responses which can limit the duration of therapy and prevent re-administration. Several strategies have demonstrated the feasibility of circumventing host immune responses, but more effective, clinically applicable procedures remain to be developed. While direct in vivo **gene therapy** strategies have generated significant progress, the results from ex vivo strategies have not been as encouraging.

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AN 2001308599 EMBASE

TI **Gene therapy** of **hemophilia**.

AU Schwaab R.; Oldenburg J.

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SO Seminars in Thrombosis and Hemostasis, (2001) 27/4 (417-424).
Refs: 50
ISSN: 0094-6176 CODEN: STHMBV

CY United States

DT Journal; General Review

FS 022 Human Genetics
025 Hematology
036 Health Policy, Economics and Management
037 Drug Literature Index

LA English

SL English

AB **Hemophilia** A and B are X-linked bleeding disorders caused by mutations within the **factor** VIII and **factor** IX genes, respectively. Although both disorders can be easily treated by substitution with concentrates of functional **factor** VIII and **factor** IX, considerable effort has been undertaken to develop a **gene therapy** for **hemophilia** in order to improve patients' life quality and reduce high costs of therapy. The principle of **gene therapy** is the introduction of an intact copy of the **factor** VIII/**factor** IX gene in somatic cells, compensating for the defective gene. To do this, **retroviral**, **adenoviral**, and adeno-associated virus (AAV) vector systems, among others, were used. Encouraged by the results of preliminary experiments using preponderant mouse and canine models, three clinical phase I studies on **hemophilia** A and B patients have been initiated, one of which has been preliminarily reported successful.

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AN 2003390008 EMBASE

TI The promise of third-generation recombinant therapy and **gene therapy**.

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SO Seminars in Hematology, (2003) 40/3 SUPPL. 3 (23-28).
Refs: 12
ISSN: 0037-1963 CODEN: SEHEA3

CY United States

DT Journal; General Review

FS 025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy

LA English

SL English

AB Recombinant **factor** VIII and IX products have well-established efficacy and safety records. However, concerns about the possibility of viral transmission have prompted efforts to develop recombinant products that are free of added human and animal proteins. The currently licensed second-generation recombinant **factor** VIII concentrates were introduced in 2000. Two new third-generation products, manufactured without any human- or animal-derived materials, are currently in development and clinical testing. As an alternative to exogenous **factor** replacement, **gene therapy** is under investigation for use in the treatment of **hemophilia**. **Gene therapy** involves the stable insertion of a functional gene for long-term expression and secretion of endogenous **factor** VIII or IX protein. Methods used to date have been based on **retroviral**, **adenoviral**, and adeno-associated viral vectors, as well as nonviral electroporation. Three phase I trials using these approaches have been completed as of 2002, and one more is ongoing. This article reviews the results of recent clinical studies investigating third-generation recombinant products and gene-based approaches to **hemophilia** treatment. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L6 ANSWER 1 OF 42 MEDLINE on STN
AN 1998039375 MEDLINE
DN PubMed ID: 9372106
TI **Gene therapy** for the **hemophilias**.
AU Fallaux F J; Hoeben R C
CS Department of Internal Medicine, University Hospital Utrecht, The Netherlands.
SO Current opinion in hematology, (1996 Sep) 3 (5) 385-9. Ref: 37
Journal code: 9430802. ISSN: 1065-6251.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199712
ED Entered STN: 19980109
Last Updated on STN: 19990129
Entered Medline: 19971223
AB This **review** discusses the progress of **gene therapy** for the **hemophilias**. The development of **gene therapy** for **hemophilia** A has been more problematic than that for **hemophilia** B. It is now well established that reduced expression of the human clotting **factor** VIII cDNA is caused by transcriptional repression. Multiple sequences within the **factor** VIII cDNA are involved. So far, attempts to improve the **factor** VIII cDNA expression have been unsuccessful. However, improved **retroviral** vectors and **adenovirus** -based vectors have been constructed that increase **factor** VIII expression. The use of these vectors has resulted in clinically relevant levels of human **factor** VIII in mice and **hemophilic** dogs. Thus, **gene therapy** for **hemophilia** A has reached the same developmental stage as that for **hemophilia** B. If further improvements can increase the persistence of expression and decrease the immunologic responses, phase I clinical trials in human individuals can be considered.